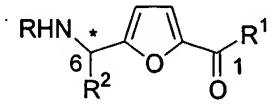
SYNTHESIS OF CHIRAL FURAN AMINO ACIDS AS NOVEL PEPTIDE BUILDING BLOCKS

FIELD OF INVENTION

The present invention relates to stereoselective chiral furan amino acids, an important class of peptide based molecules having a general structure as shown in 1 in Formula 1, and process for preparing the same. More Particularly, the novel chiral furan amino acids, carry a chiral center at the amino terminal with substituent resembling the side-chains of natural amino acids and stereoselective synthesis of these molecules in either *R*- or *S*-enantiomeric forms. The starting materials are being used chiral *N*-terminal-protected amino aldehydes derived from the corresponding *N*-terminal-protected protected L- or D-amino acids.



FORMULA 1

* (C6 is either *R* or *S*)

Wherein;

R = H, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 9-fluorenylmethyl (Fmoc), acetyl or salts such as HCl.H, $CF_3COOH.H$ and others;

R^1 = -OH, -O-alkyl, -O-arylalkyl, -amine, -alkylamine, -arylalkylamine, and others

R^2 = CH_3-, $(CH_3)_2CH$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, alkyl groups, $(OR^3)CH_2$-, $CH_3(OR^3)CH$-, $(R^3S)CH_2$-, $CH_3SCH_2CH_2$-, $(RHN)CH_2CH_2CH_2CH_2$-, $(CONH_2)CH_2$-, $(CONH_2)CH_2CH_2$-, $(CO_2R^4)CH_2$-, $(CO_2R^4)CH_2CH_2$-, Ph-, Ar-, $PhCH_2$-, $ArCH_2$-, Phenylalkyl-, arylalkyl-, (indolyl)CH_2-, (imidazolyl)CH_2-, and all other amino acid side-chains

R^3 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, CO(alkyl), CO(arylalkyl), SO_3H, PO_3H_2, silyl and others

R^4 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, and others

R-R^2 = -$(CH_2)_n$- (n = 2, 3, 4...)

BACKGROUND OF THE INVENTION

In search of new molecular entities for discovering new drugs and materials, organic chemists are looking for innovative approaches that try to imitate nature in assembling quickly large number of distinct and diverse molecular structures from 'nature-like' and yet unnatural designer building blocks using combinatorial approach. This has become necessary today as it is being increasingly felt that natural products, or

natural product based leads hold better promises for discovering new molecular entities as drugs (Rouhi, A. M. *C&En* **2003**, *81*(41), 77-91).[1] Peptide based molecules can play very important roles, in this aspect, in the development of new drugs. However, the use of peptides as drugs is limited by their low physiological stability in the gastrointestinal tract, loss of their original conformation once truncated from the native protein and their intrinsic flexibility because of which it is difficult to restrict short linear peptides in any particular conformation required to bind effectively to receptors. To overcome these problems, conformationally rigid non-peptide "scaffolds" can be inserted in the appropriate sites in the peptides to produce the specific secondary structure required for binding to the corresponding receptor. Compounds made of such unnatural building blocks are also expected to be more stable toward proteolytic cleavage in physiological systems than their natural counterparts. The unnatural building blocks developed for this purpose should be carefully designed to manifest the structural diversities of the monomeric units used by nature like amino acids, carbohydrates and nucleosides to build its arsenal.

In recent years, furan amino acid, 5-(aminomethyl)-2-furoic acid (Chakraborty, T. K. et al *Tetrahedron Letters* **2002**, *43*, 1317–1320)[2] and pyrrole amino acid, 5-(aminomethyl)-1*H*-pyrrole-2-carboxylic acid (Chakraborty, T. K. et al *Tetrahedron Letters* **2002**, *43*, 2589–2592; Chakraborty, T. K. et al *Tetrahedron Letters* **2003**, *44*, 471–473),[3] have emerged as versatile templates that have been used as conformationally constrained scaffolds in peptidomimetic studies and as important class of synthetic monomers leading to de novo oligomeric libraries. These furan amino acid and pyrrole amino acid are designer building blocks bearing both amino and carboxyl functional groups on the regular furan and pyrrole frameworks, respectively, at C2 and C5 positions. There are several advantages of these building blocks. The rigid furan and pyrrole rings of these molecules make them ideal candidates as non-peptide scaffolds in peptidomimetics where they can be easily incorporated by using their carboxyl and amino termini utilizing well-developed solid-phase or solution-phase peptide synthesis methods. At the same time, it allows efficient exploitation of the structural constraints of these molecules to create the desired folded structures in small peptides required to bind to their receptors. The insertion of these scaffolds can also influence the hydrophobic/hydrophilic nature of the resulting peptidomimetic compounds.

Introduction of a chiral center in the amino terminus of these furan amino acids gives rise to an additional combinatorial site in these multifunctional building blocks that will not only help to induce desired secondary structure in peptides, but will also allow to mimic the side-chains of natural amino acids influencing the hydrophobicity / hydrophilicity of the resulting peptidomimetic molecules.While synthesis of unsubstituted 5-(aminomethyl)-2-furoic acid has been reported starting from fructose (Chakraborty, T. K. et al *Tetrahedron Letters* **2002**, *43*, 1317–1320),[2] introduction of a chiral center in its C6 position required a different approach.

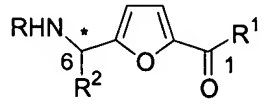
Development of a robust synthetic strategy to construct these molecules in enantiomerically pure forms will allow their wide-ranging applications in peptidomimetic studies. The strategy adopted here allows synthesis of these molecules in either *R*- or *S*-enantiomeric forms depending on the chiralities of the starting amino acids.

The following abbreviation are used with the following meanings: CSA: camphor sulphonic acid; DMSO: dimethyl sulfoxide; PCC: pyridinium chlorochromate; Boc: tert-butoxycarbonyl; FmocOSu: 9-fluorenylmethyl *N*-succinimidyl carbonate; TFA: trifluoroacetic acid; DCC =*N,N'*-dicyclohexylcarbodiimide; HOBt = 1-hydroxybenzotrazole.

Amino acids are denoted by L or D appearing before the symbol and separated from it by hyphen.

OBJECTIVES OF THE INVENTION

The main objective of the invention is to provide stereoselective chiral furan amino acids, an important class of peptide based molecules having a general structure as shown in 1 in Formula 1.



* (C6 is either *R* or *S*)

Wherein;

R = H, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 9-fluorenylmethyl (Fmoc), acetyl or salts such as HCl.H, CF_3COOH.H and others;

R^1 = -OH, -O-alkyl, -O-arylalkyl, -amine, -alkylamine, -arylalkylamine, and others

R^2 = CH_3-, $(CH_3)_2CH$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, alkyl groups, $(OR^3)CH_2$-, $CH_3(OR^3)CH$-, $(R^3S)CH_2$-, $CH_3SCH_2CH_2$-, $(RHN)CH_2CH_2CH_2CH_2$-, $(CONH_2)CH_2$-,

$(CONH_2)CH_2CH_2$-, $(CO_2R^4)CH_2$-, $(CO_2R^4)CH_2CH_2$-, Ph-, Ar-, $PhCH_2$-, $ArCH_2$-, Phenylalkyl-, arylalkyl-, (indolyl)CH_2-, (imidazolyl)CH_2-, and all other amino acid side-chains

R^3 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, CO(alkyl), CO(arylalkyl), SO_3H, PO_3H_2, silyl and others

R^4 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, and others

R-R^2 = -$(CH_2)_n$- (n = 2, 3, 4...).

Another objective of the present invention is to provide a process for preparing novel chiral furan amino acids, carry a chiral center at the amino terminal with substituent resembling the side-chains of natural amino acids and stereoselective synthesis of these molecules in either *R*- or *S*-enantiomeric forms.

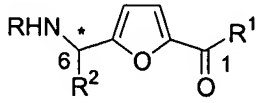
Yet another objective of the present invention is to provide novel furan amino acid peptide based molecules that carry a chiral center at the amino terminal, giving rise to an additional combinatorial site in these multifunctional molecules which can be used in various peptidomimetic studies to induce conformational constraints in small peptides.

SUMMARY OF THE INVENTION

The present invention provides a chiral furan amino acids, in enantiomerically pure forms, either *R* or *S*. The starting materials are being used chiral *N*-terminal-protected amino aldehydes derived from the corresponding *N*-terminal-protected protected L- or D-amino acids. The present invention also relates to a process for preparing these chirally substituted furan amino acids constitute an important class of conformationally constrained peptide based molecules that can be used as dipeptide isosteres in peptidomimetic studies.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly the present invention provides an unnatural chiral furan amino acids carrying natural amino acid side-chains in C6-position and having a general structure **1** as shown in **Formula 1**.



1

Formula 1

* (Stereochemistry of C6 is either *R* or *S*)

Wherein;

R = H, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 9-fluorenylmethyl (Fmoc), acetyl or salts such as HCl, $CF_3COOH.H$ and others;

R^1 = -OH, -O-alkyl, -O-arylalkyl, -amine, -alkylamine, -arylalkylamine, and others;

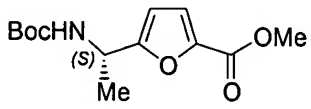
$R^2 = CH_3$-, $(CH_3)_2CH$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, alkyl groups; $(OR^3)CH_2$-, $CH_3(OR^3)CH$-, $(R^3S)CH_2$-, $CH_3SCH_2CH_2$-, $(RHN)CH_2CH_2CH_2CH_2$-; $(CONH_2)CH_2$-, $(CONH_2)CH_2CH_2$-, $(CO_2R^4)CH_2$-, $(CO_2R^4)CH_2CH_2$-, Ph-, Ar-; $PhCH_2$-, $ArCH_2$-, Phenylalkyl-, arylalkyl-, (indolyl)CH_2-, (imidazolyl)CH_2-, and all other amino acid side-chains;

R^3 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, CO(alkyl), CO(arylalkyl), SO_3H, PO_3H_2, silyl and others;

R^4 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, and others;

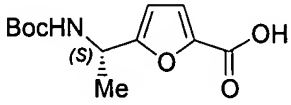
R-R^2 = -$(CH_2)_n$- (n = 2, 3, 4...);

In an embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = Me, R^2 = Me and R = Boc having a structural formula **2** shown here below



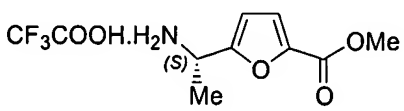
2

In another embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OH, R^2 = Me and R = Boc having a structural formula **3** shown here below

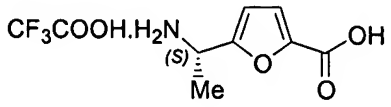


3

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OMe, R^2 = Me and R = $CF_3COOH.H$ having a structural formula **4** shown here below

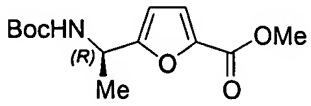


In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OH, R^2 = Me and R = $CF_3COOH.H$ having a structural formula **5** shown here below



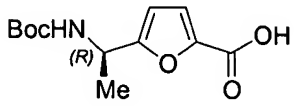
5

In still another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OMe, R^2 = Me and R = Boc having a structural formula **6** shown here below



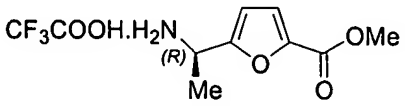
6

In a further embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OH, R^2 = Me and R = Boc having a structural formula **7** shown here below



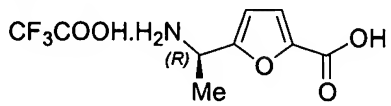
7

In one more embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OMe, R^2 = Me and R = $CF_3COOH.H$ having a structural formula **8** shown here below



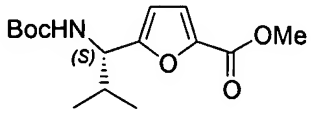
8

In one another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OH, R^2 = Me and R = $CF_3COOH.H$ having a structural formula **9** shown here below



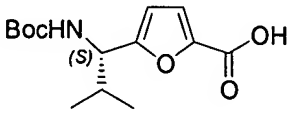
9

In another embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OMe, R^2 = $CHMe_2$ and R = Boc having a structural formula **10** shown here below



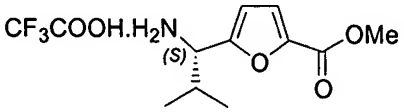
10

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OH, R^2 = $CHMe_2$ and R = Boc having a structural formula **11** shown here below



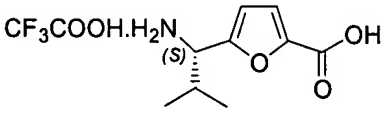
11

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OMe, R^2 = $CHMe_2$ and R = $CF_3COOH.H$ having a structural formula **12** shown here below



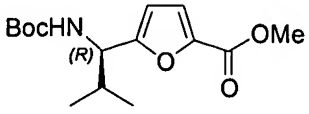
12

In one more embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OH, R^2 = $CHMe_2$ and R = $CF_3COOH.H$ having a structural formula **13** shown here below



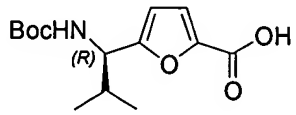
13

In one another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OMe, R^2 = $CHMe_2$ and R = Boc having a structural formula **14** shown here below:



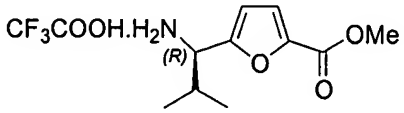
14

In still another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are $R^1 = OH$, $R^2 = CHMe_2$ and R = Boc having a structural formula **15** shown here below



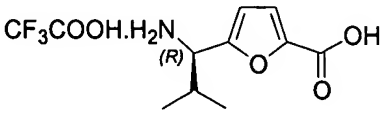
15

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are $R^1 = OMe$, $R^2 = CHMe_2$ and R = $CF_3COOH.H$ having a structural formula **16** shown here below



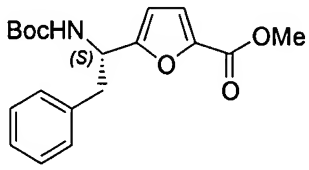
16

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are $R^1 = OH$, $R^2 = CHMe_2$ and R = $CF_3COOH.H$ having a structural formula **17** shown here below



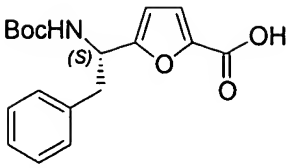
17

In a further embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are $R^1 = OMe$, $R^2 = CH_2Ph$ and R = Boc having a structural formula **18** shown here below



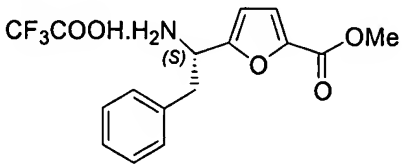
18

In a further more embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are $R^1 = OH$, $R^2 = CH_2Ph$ and R = Boc having a structural formula **19** shown here below



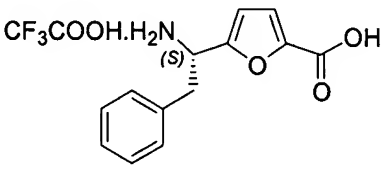
19

In one more embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OMe, R^2 = CH_2Ph and R = $CF_3COOH.H$ having a structural formula **20** shown here below



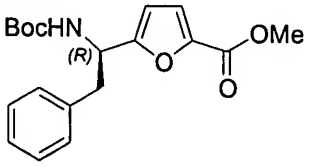
20

In another embodiment of the present invention, wherein if the stereochemistry of C6 is *S* and the substitutions are R^1 = OH, R^2 = CH_2Ph and R = $CF_3COOH.H$ having a structural formula **21** shown here below



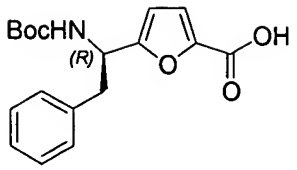
21

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OMe, R^2 = CH_2Ph and R = Boc having a structural formula **22** shown here below



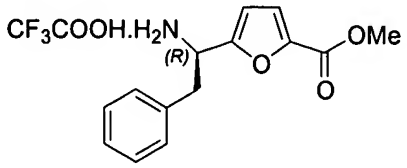
22

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OH, R^2 = CH_2Ph and R = Boc having a structural formula **23** shown here below



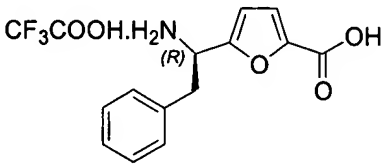
23

In yet another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OMe, R^2 = CH_2Ph and R = $CF_3COOH.H$ having a structural formula **24** shown here below



24

In a still another embodiment of the present invention, wherein if the stereochemistry of C6 is *R* and the substitutions are R^1 = OH, R^2 = CH_2Ph and R = $CF_3COOH.Hc$ having a structural formula **25** shown here below



25

In yet another embodiment of the present invention, wherein *N*-Fmoc-protected furan amino acid is obtained by treatment with FmocOSu in dioxane-water in the ration of 1:1.

In still another embodiment of the present invention, wherein if structure **1** with substitution R = Boc, R^1 = OH, R^2 = Me and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 1:9 MeOH/$CHCl_3$ with 1% AcOH); $[\alpha]_D^{23}$ = –52.8 (*c* 1.14, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.17 (br d, *J* = 2.2 Hz, 1 H, aromatic), 6.29 (d, *J* = 2.2 Hz, 1 H, aromatic), 5.04 (br m, 1 H, N*H*), 4.93 (br m, 1 H, C*H*NH), 1.48 (d, *J* = 6.59 Hz, 3 H, CH3), 1.42 (s, 9 H, *t*-butyl) and yield up to 98%.

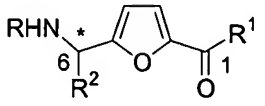
In one more embodiment of the present invention, wherein if structure **1** with substitution R = Boc, R^1 = OH, R^2 = $CHMe_2$ and 6*S* stereochemistry, has the following characteristics: R_f = 0.5 (silica, 1:9 MeOH/$CHCl_3$ with 1% AcOH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.18 (br 1 H, one of the furan ring protons), 6.39 (br, 1 H, one of the

furan ring protons), 5.09 (br, 1 H, N*H*), 4.61 (br, 1 H, C*H*NH), 2.2 (m, 1 H, C*H*$(CH_3)_2$), 1.42 (s, 9 H, *t*-butyl), 0.95 (d, J = 6.69 Hz, 3 H, CH_3), 0.89 (d, J = 6.69 Hz, 3 H, CH_3) and yield up to 88%.

In another embodiment of the present invention, wherein if structure **1** with substitution R = Boc, R^1 = OH, R^2 = CH_2Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.5 (silica, 10 MeOH/$CHCl_3$ with 1% AcOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (m, 5 H, aromatic protons), 7.05 (br, 1 H, one of the furan ring protons), 6.12 (br, 1 H, one of the furan ring protons), 5.03 (m, 2 H, N*H* & C*H*NH), 3.16 (m, 2 H, CH_2Ph), 1.39 (s, 9 H, *t*-butyl) and yield up to 92%.

In yet another embodiment of the present invention, wherein if structure **1** with substitution R = Boc, R^1 = OH, R^2 = Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.5 (silica, 10% MeOH/$CHCl_3$ with 1% AcOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 7.15 (br, 1 H, one of the furan ring protons), 6.21 (br, 1 H, one of the furan ring protons), 5.85 (br, 1 H, C*H*NH), 5.43 (br, 1 H, N*H*), 1.44 (s, 9 H, *t*-butyl) and yield up to 90%.

In a further more embodiment of the present invention relates to a process for preparing unnatural chiral furan amino acids carrying natural amino acid side-chains in C6-position and having a general structure as shown in structure **1.**



1

* (Stereochemistry of C6 is either *R* or *S*)

Wherein; R = H, Boc, Cbz, Fmoc, acetyl or salts such as HCl.H, CF_3COOH.H and others;

R^1 = -OH, -O-alkyl, -O-arylalkyl, -amine, -alkylamine, -arylalkylamine, and others;

R^2 = CH_3-, $(CH_3)_2CH$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, alkyl groups; $(OR^3)CH_2$-, $CH_3(OR^3)CH$-, $(R^3S)CH_2$-, $CH_3SCH_2CH_2$-, $(RHN)CH_2CH_2CH_2CH_2$-; $(CONH_2)CH_2$-, $(CONH_2)CH_2CH_2$-, $(CO_2R^4)CH_2$-, $(CO_2R^4)CH_2CH_2$-, Ph-, Ar-; $PhCH_2$-, $ArCH_2$-, Phenylalkyl-, arylalkyl-, (indolyl)CH_2-, (imidazolyl)CH_2-, and all other amino acid side-chains;

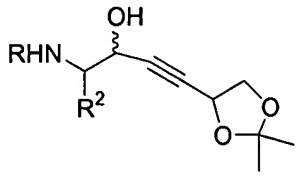
R^3 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, CO(alkyl), CO(arylalkyl), SO_3H, PO_3H_2, silyl and others;

R^4 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, and others;

$R\text{-}R^2 = -(CH_2)_n-$ (n = 2, 3, 4...);

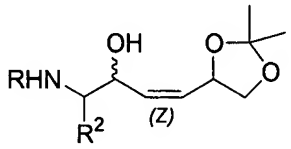
said process comprising the steps of:

a) addition of Li-acetylide, prepared *in-situ* by reacting 3,4-*O*-isopropylidene-1,1-dibromobut-1-en-3,4-diol **3** with n-BuLi, to the chiral *N*-protected amino aldehyde **2** to obtain the propargyl alcohol adduct **4** as a mixture of isomers having the structure



4
propargyl alcohol adduct

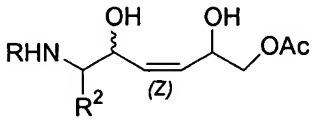
b) selective hydrogenation of the acetylenic moiety to a *cis* double bond using P2-Ni to get the *cis*-allylic alcohol intermediate **5** having the structure



5
cis-allylic alcohol intermediate

c) treating **5** with acid to deprotect the acetonide and to furnish an intermediate triol

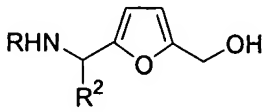
d) selective acylation of the primary hydroxyl group of the triol from of step (c) to obtain the "*cis*-2-butene-1,4-diol" intermediate **6** having the structure



6
"*cis*-2-butene-1,4-diol" intermediate

e) oxidation of the "*cis*-2-butene-1,4-diol" intermediate **6** using pyridinium chlorochromate (PCC) to construct the furan ring

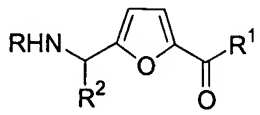
f) deprotection of the intermediate acetate from step (e) in presence of anhydrous K_2CO_3 to obtain the chiral furanyl alcohol intermediate **7** having the structure



7
chiral furanyl alcohol intermediate

g) oxidation of the primary hydroxyl of the chiral furanyl alcohol intermediate **7** using Swern oxidation process or SO_3-py complex to obtain an aldehyde

h) further oxidation of the aldehyde intermediate from step (g) using $NaClO_2$-H_2O_2 to obtain the desired acid **1** (R^1 = OH) having the structure



1
Chiral furan amino acid

i) transformation of the acid from step (h) into (a) an ester (i) on treatment with CH_2N_2 in ether (**1**: R^1 = OMe), or (ii) an alcohol in the presence of acid (**1**: R^1 = O-alkyl etc.); (b) an amide on treatment with an amine in presence of DCC and HOBt (**1**: R^1 = -amine, -alkylamine, -arylalkylamine).

In an embodiment of the present invention, wherein if structure **4** with substitution R = Boc, R^2 = Me and 6*S* stereochemistry, has the following characteristics: R_f = 0.5 (silica, 2:3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73-4.68 (ddd, J = 6.04, 3.78, 1.51 Hz, 1 H, C*H*OH), 4.65- 4.62 (d, J = 8.31 Hz, 1 H, N*H*), 4.36-4.32 (ddd, J = 6.79, 5.29, 1.51 Hz, 1 H, C*H*CH_2), 4.15-4.09 (dd, J = 6.79, 6.04 Hz, 1 H, one of the CH_2 protons), 3.91-3.86 (dd, J = 6.04, 5.29 Hz, 1 H, one of the CH_2 protons), 3.83- 3.76 (m, 1 H, C*H*NH), 2.89 (bs, 1 H, O*H*), 1.45 (s, 3 H, acetonide methyl protons), 1.442 (s, 9 H, *t*-butyl protons), 1.354 (s, 3 H, acetonide methyl protons), 1.247-1.225 (d, J = 6.79 Hz, 3 H, C*H*$_3$) and yield up to 60 %.

In another embodiment of the present invention, wherein structure **4** with substitution R = Boc, R^2 = $CHMe_2$ and 6*S* stereochemistry, has the following characteristics: R_f = 0.5 (silica, 40% EtOAc / Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ

4.7 (m, 1 H, C*H*OH), 4.59 (d, J = 9.07 Hz, 1 H, N*H*), 4.12 (m, 1 H, C*H*CH_2), 3.88 (m, 2 H, CH_2), 3.54 (m, 1 H, C*H*NH), 1.78 (m, 1 H, C*H*$(CH_3)_2$), 1.46 (s, 9 H, *t*-butyl), 1.45 (s, 6 H, acetonide protons), 0.99 (d, J = 6.8 Hz, 6 H, CH_3) and yield up to 63%.

In one more embodiment of the present invention, wherein if structure **4** with substitution R = Boc, R^2 = CH_2Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (m, 5 H, aromatic protons), 4.82-4.65 (m, 2 H, C*H*OH & N*H*), 4.37 (br, 1 H, C*H*NH), 4.19-4.06 (m, 2 H, C*H* & one of the CH_2), 3.9 (m, 1 H, one of the CH_2), 2.91 (m, 2 H, CH_2Ph), 1.39-1.38 (m, 15 H, *t*-butyl & acetonide methyls) and yield up to 65%.

In another embodiment of the present invention, wherein if structure **4** with substitution R = Boc, R^2 = Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 5.27-5.18 (m, 2 H, C*H*OH & N*H*), 5 (m, 1 H, C*H*NH), 4.94 (m, 1 H, C*H*), 4.03 (m, 2 H, CH_2), 1.44 (s, 9 H, *t*-butyl), 1.41 (s, 6 H, acetonide methyls) and yield up to 62%.

In yet another embodiment of the present invention, wherein if structure **5** with substitution R = Boc, R^2 = Me and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 2:3 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.62-5.55 (m, 2 H, olefinic protons), 4.92-4.68 (m, 2 H, C*H*OH), 4.36-4.27 (bs, 1 H, N*H*), 4.15-4.05 (m, 2 H, CH_2OH), 3.71-3.61 (m, 1 H, C*H*), 3.06 (bs, 1 H, O*H*), 1.44 (s, 9 H, *t*-butyl protons), 1.40 (s, 3 H, acetonide methyl protons), 1.36 (s, 3 H, acetonide methyl protons), 1.18- 1.15 (d, J = 6.69 Hz, 3 H, methyl protons) and yield up to 70%.

In yet another embodiment of the present invention, wherein if structure **5** with substitution R = Boc, R^2 = $CHMe_2$ and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 30% EtOAc /Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 1 H, olefinic proton), 5.54 (m, 1 H, olefinic proton), 4.71 (bs, 1 H, N*H*), 4.5 (m, 1 H, C*H*OH), 4.09 (m, 1 H, C*H*), 3.55 (m, 2 H, CH_2), 3.24 (m, 1 H, C*H*NH), 1.94 (m, 1 H, C*H*$(CH_3)_2$), 1.44 (s, 9 H, *t*-butyl), 1.43 (s, 6 H, acetonide methyls), 1.0 (d, J = 6.8 Hz, 3 H, CH_3), 0.93 (d, J = 6.8 Hz, 3 H, CH_3) and yield up to 60%.

In yet another embodiment of the present invention, wherein if structure **5** with substitution R = Boc, R^2 = CH_2Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ

7.21 (m, 5 H, aromatic protons), 5.82-5.55 (m, 2 H, olefinic protins), 4.78 (m, 1 H, N*H*), 4.62-4.34 (m, 2 H, C*H*OH & C*H*), 4.06 (m, 1 H, C*H*NH), 3.51 (m, 2 H, CH_2), 2.85 (m, 2 H, CH_2Ph), 1.39-1.32 (m, 15 H, *t*-butyl & acetonide methyls) and yield up to 65%.

In yet another embodiment of the present invention, wherein if structure **5** with substitution R = Boc, R^2 = Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 40% EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 5 H, aromatic protons), 5.87-5.55 (m, 2 H, olefinic protons), 5.25 (m, 2 H, C*H*OH, N*H*), 4.99 (m, 1 H, C*H*NH), 4.58 (m, 1 H, C*H*), 3.90 (m, 2 H, CH_2), 1.44 (s, 9 H, *t*-butyl), 1.41 (s, 6 H, acetonide methyls) and yield up to 70%.

In still another embodiment of the present invention, wherein if structure **6** with substitution R = Boc, R^2 = Me and 6*S* stereochemistry, has the following characteristics: R_f = 0.6 (silica, 1:9 methanol/chloroform); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.66-5.46 (two dd, *J* = 11.89, 6.69 Hz, 2 H, olefinic protons), 4.90-4.85 (d, *J* = 8.92 Hz, 1 H, N*H*), 4.66-4.59 (dt, *J* = 6.69, 4.46 Hz, 1 H, C*H*OH), 4.41-4.36 (ddd, *J* = 6.69, 5.02, 4.46 Hz, 1 H, C*H*OH), 4.16-3.98 (two dd, *J* = 11.15, 6.69 and 11.15, 4.46 Hz, 2 H, CH_2OAc), 2.09 (s, 3 H, CH_3CO), 1.44 (s, 9 H, *t*-butyl), 1.20- 1.17 (d, *J* = 6.69 Hz, 3 H, CH_3) and yield up to 93%.

In still one more embodiment of the present invention, wherein if structure **6** with substitution R = Boc, R^2 = $CHMe_2$ and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 10% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (dd, *J* = 11.33, 7.93 Hz, 1 H, olefinic proton), 5.54 (dd, *J* = 11.33, 8.31 Hz, 1 H, olefinic proton), 4.72-4.67 (m, 1 H, C*H*OH), 4.4 (dd, *J* = 7.93, 6.8 Hz, 1 H, C*H*), 4.18 (dd, *J* = 11.33, 3.4 Hz, 1 H one of the CH_2), 3.93 (dd, *J* = 11.33, 7.55 Hz, 1 H, one of the CH_2), 2.1 (s, 3 H, COCH_3), 2 (m, 1 H, C*H*$(CH_3)_2$), 1.42 (s, 9 H, *t*-butyl), 0.97 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.92 (d, *J* = 6.8 Hz, 3 H, CH_3) and yield up to 80%.

In yet another embodiment of the present invention, wherein if structure **6** with substitution R = Boc, R^2 = CH_2Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 10% MeOH/$CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21 (m, 5 H, aromatic protons), 5.68-5.45 (m, 2 H, olefinic protons), 4.65 (m, 2 H, C*H*OH & N*H*), 4.45 (m, 1 H, C*H*OH), 4.05 (m, 2 H, CH_2), 3.8 (m, 1 H, C*H*NH), 2.85 (m, 2 H, CH_2Ph), 2.04 (s, 3 H, COCH_3), 1.25 (m, 15 H, *t*-butyl) and yield up to 90%.

In yet another embodiment of the present invention, wherein if structure **6** with substitution R = Boc, R^2 = Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 10% MeOH/$CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 5.87-5.55 (m, 2 H, olefinic protons), 5.25 (m, 2 H, C*H*OH & N*H*), 4.85 (m, 1 H, C*H*NH), 4.61 (m, 1 H, C*H*OH), 4.21 (m, 2 H, CH_2), 2.1 (s, 3 H, COCH_3), 1.44 (s, 9 H, *t*-butyl) and yield up to 85%.

In a further embodiment of the present invention, wherein if structure **7** with substitution R = Boc, R^2 = Me and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 1:1 ethyl acetate/hexane); $[\alpha]_D^{23}$ = –59.9 (*c* 1.76, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.17-6.14 (d, *J* = 2.97 Hz, 1 H, one of the ring protons), 6.08-6.04 (d, *J* = 2.97 Hz, 1 H, one of the ring protons), 4.86-4.71 (bs, 2 H, N*H* and C*H*), 4.52 (s, 2 H, CH_2OH), 2.14- 1.93 (bs, 1 H, O*H*) 1.48- 1.43 (s,12 H, *t*-butyl group and methyl protons) and yield up to 98%.

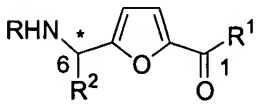
In a further more embodiment of the present invention, wherein if structure **7** with substitution R = Boc, R^2 = $CHMe_2$ and 6*S* stereochemistry, has the following characteristics: R_f = 0.5 (silica, 30% EtOAc/Hexane); $[\alpha]_D^{23}$ = –59.9 (*c* 1.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, *J* = 2.93 Hz, 1 H, one of the furan ring protons), 6.06 (d, *J* = 2.93 Hz, 1 H, one of the furan ring protons), 4.84 (d, *J* = 8.79 Hz, 1 H, N*H*), 4.53 (s, 2 H, CH_2OH), 4.52 (m, 1 H, C*H*NH) 2.09 (m, 1 H, C*H*(CH_3)$_2$), 1.44 (s, 9 H, *t*-butyl), 0.94 (d, , *J* = 6.59 Hz, 3 H, CH_3), 0.88 (d, , *J* = 6.59 Hz, 3 H, CH_3) and yield up to 95%.

In yet another embodiment of the present invention, wherein if structure **7** with substitution R = Boc, R^2 = CH_2Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.5 (silica, 40% EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.2 (m, 3 H, aromatic protons), 7.02 (m, 2 H, aromatic protons), 6.12 (d, *J* = 2.97 Hz, 1 H, one of the furan ring protons), 5.93 (d, *J* = 2.97 Hz, 1 H, one of the furan ring protons), 4.94 (m, 1 H, C*H*NH), 4.81 (d, *J* = 8.92 Hz, 1 H, N*H*), 4.53 (s, 2 H, CH_2OH), 3.09 (d, *J* = 6.69 Hz, 2 H, CH_2Ph), 1.39 (s, 9 H, *t*-butyl) and yield up to 96%.

In still another embodiment of the present invention, wherein if structure **7** with substitution R = Boc, R^2 = Ph and 6*S* stereochemistry, has the following characteristics: R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 6.16 (d, *J* = 3.05 Hz, 1 H, one of the furan ring protons), 6.02 (d, *J* =

3.05 Hz, 1 H, one of the furan ring protons), 5.87 (br, 1 H, N*H*), 5.25 (d, J = 8.52 Hz, 1 H, C*H*NH), 4.51 (s, 2 H, CH_2OH), 1.44 (s, 9 H, *t*-butyl) and yield up to 95%.

The present invention relates to the stereoselective construction of chiral furan amino acids, an important class of peptide building blocks, having a general structure as shown in **1** in **Formula 1**, in 8 steps (9 steps, for ester or amide) (**Scheme 1**) using chiral *N*-terminal-protected amino aldehydes as starting materials that could also be derived from the corresponding *N*-terminal-protected protected L- or D-amino acids, like for example, Boc-L-Ala-OH, Boc-D-Ala-OH, Boc-L-Phe-OH, Boc-D-Phe-OH, Boc-L-Val-OH, Boc-L-Val-OH, Boc-L-Leu-OH, Boc-L-Leu-OH, Boc-L-Ile-OH, Boc-D-Ile-OH, Boc-L-Ser(Bzl)-OH, Boc-D-Ser(Bzl)-OH, Boc-L-Thr(Bzl)-OH, Boc-D-Thr(Bzl)-OH, Boc-L-Tyr(Bzl)-OH, Boc-D-Tyr(Bzl)-OH, Fmoc-L-Ala-OH, Fmoc-D-Ala-OH, Fmoc-L-Phe-OH, Fmoc-D-Phe-OH, Fmoc-L-Val-OH, Fmoc-L-Val-OH, Fmocc-L-Leu-OH, Fmoc-L-Leu-OH, Fmoc-L-Ile-OH, Fmoc-D-Ile-OH, Fmoc-L-Ser(But)-OH, Boc-D-Ser(But)-OH, Fmoc-L-Thr(But)-OH, Fmoc-D-Thr(But)-OH, Fmoc-L-Tyr(But)-OH, Fmoc-D-Tyr(But)-OH and other appropriately protected amino acids, by converting them first to Weinreb amide, followed by reduction to aldehyde using $LiAlH_4$ (Fehrentz, J.-A. et al *Synthesis* **1983**, 676-678).[4]



1

* (C6 is either *R* or *S*)

wherein;

R = H, tert-butoxycarbonyl (Boc), benzyloxycarbonyl (Cbz), 9-fluorenylmethyl (Fmoc), acetyl or salts such as HCl.H, CF_3COOH.H and others;

R^1 = -OH, -O-alkyl, -O-arylalkyl, -amine, -alkylamine, -arylalkylamine, and others

R^2 = CH_3-, $(CH_3)_2CH$-, $(CH_3)_2CHCH_2$-, $CH_3CH_2CH(CH_3)$-, alkyl groups, $(OR^3)CH_2$-, $CH_3(OR^3)CH$-, $(R^3S)CH_2$-, $CH_3SCH_2CH_2$-, $(RHN)CH_2CH_2CH_2CH_2$-, $(CONH_2)CH_2$-, $(CONH_2)CH_2CH_2$-, $(CO_2R^4)CH_2$-, $(CO_2R^4)CH_2CH_2$-, Ph-, Ar-, $PhCH_2$-, $ArCH_2$-, Phenylalkyl-, arylalkyl-, (indolyl)CH_2-, (imidazolyl)CH_2-, and all other amino acid side-chains

R^3 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, CO(alkyl), CO(arylalkyl), SO_3H, PO_3H_2, silyl and others

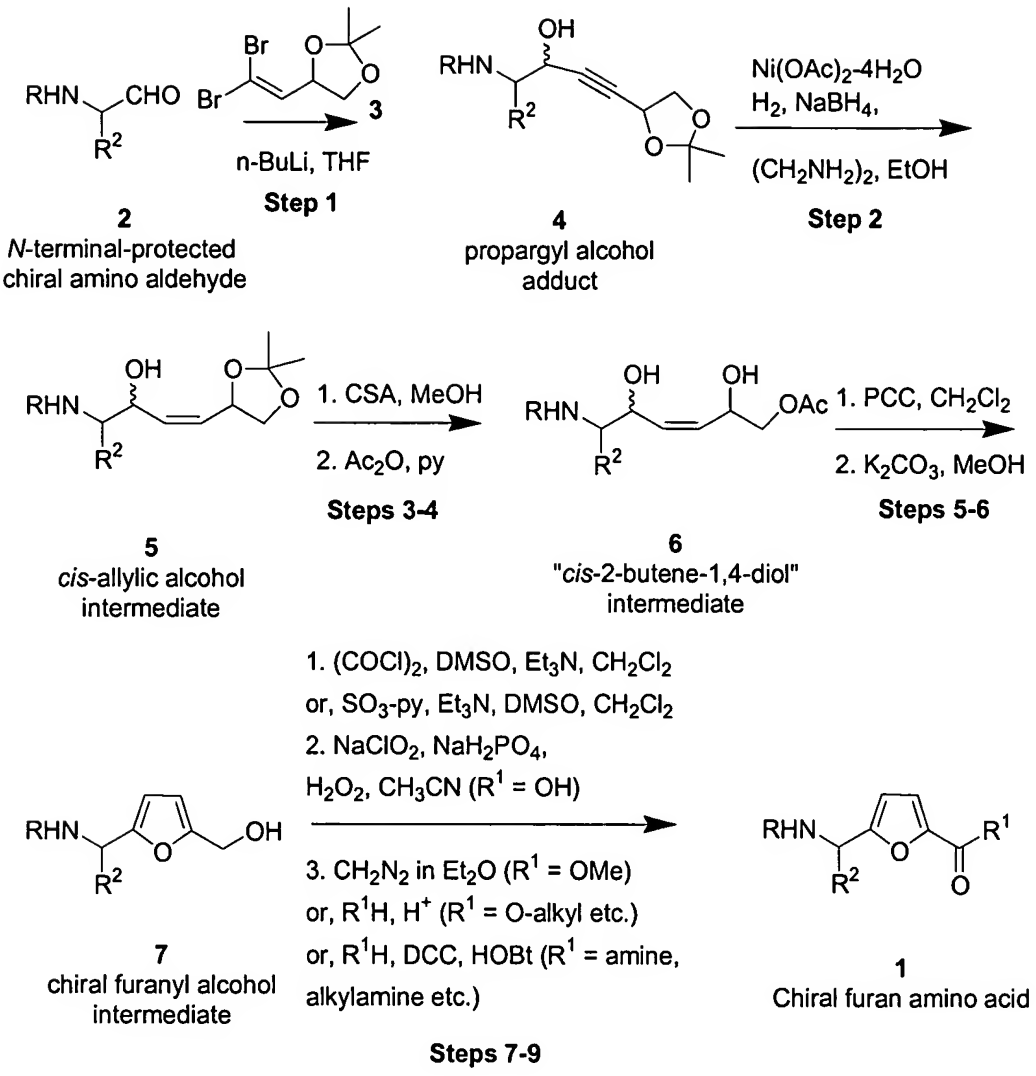
R^4 = H, *tert*-butyl, alkyl, benzyl, arylCH_2, and others

R-R^2 = -$(CH_2)_n$- (n = 2, 3, 4...)

Formula 1

Synthesis of chiral furan amino acids

The synthetic protocol developed in the present invention for the stereoselective synthesis of C6-substituted furan amino acids, **1** in **Formula 1**, may suitably be employed to synthesize any of the two enantiomers, *R* or *S*, in optically pure form. The details of the synthesis involving 8 steps (9 steps, for ester or amide) are shown in **Scheme 1**. Treatment of chiral *N*-protected amino aldehyde **2** derived from the corresponding amino acid (Reetz, M. T. etal *Org. Synth.* **1998**, *76*, 110; Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121-1162)[5] with the Li-acetylide prepared *in-situ* by reacting 3,4-*O*-isopropylidene-1,1-dibromobut-1-en-3,4-diol **3** (Gung, B. W. etal *J. Org. Chem.* **2003**, *68*, 5956-5960)[6] with n-BuLi, gave the propargyl alcohol adduct **4** as a mixture of isomers. Cis-hydrogenation of **4** using P2-Ni (Brown, C. A. et al *J. Chem. Soc., Chem. Commun.* **1973**, 553; Brown, C. A. et al *J. Org. Chem.* **1973**, *38*, 2226)[7] provided the *cis*-allylic alcohol intermediate **5**. Treatment of **5** with acid led to the deprotection of the acetonide and the primary hydroxyl was selectively protected as acetate to get the "*cis*-2-butene-1,4-diol" intermediate **6**. The resulting "*cis*-2-butene-1,4-diol" moiety of **6** was next transformed into a furan ring on oxidation with pyridinium chlorochromate (PCC) (Nishiyama, H. et al *Chemistry Lett.* **1981**, 1363-1366)[8] which was followed by the treatment of the intermediate with anhydrous K_2CO_3 to deprotect the acetate to give the chiral furanyl alcohol intermediate **7**. Finally, a two-step oxidation process, (i) Swern oxidation or oxidation by SO_3-py complex to aldehyde, and (ii) oxidation of the aldehyde to acid using $NaClO_2$-H_2O_2, converted the primary hydroxyl group of **7** into the acid functionality (**1**: R^1 = OH), which was transformed into (a) an ester (i) on treatment with CH_2N_2 in ether (**1**: R^1 = OMe), or (ii) an alcohol in presence of acid (**1**: R^1 = O-alkyl etc.); (b) an amide on treatment with an amine in presence of DCC and HOBt (**1**: R^1 = -amine, -alkylamine, -arylalkylamine).



Scheme 1: Synthesis of chiral C6-substituted furan amino acids 1 (Formula 1).

Example 1: Process for preparing chiral furan amino acid 1 wherein C6 stereochemistry is *S* and the substitutions are R = Boc, R^1 = OH, R^2 = Me

Step 1: Preparation of the propargyl alcohol adduct 4 (R = Boc, R^2 = Me with 6*S* stereochemistry)

To a solution of the dibromo compound **3** (7.82 g) in THF (110 mL) at –78 °C, nBuLi (1.6 M in hexane, 32.5 mL) was slowly added with stirring. Stirring was continued at –78 °C for 30 minutes and then at room temperature for another 30 minutes, recooled to –78 °C and the aldehyde *N*-Boc-L-alaninal (**2**: R = Boc, R^2 = Me with 6*S* stereochemistry) (4.0 g), dissolved in THF (20 mL), was added. After 30 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl solution.

The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were removed in rotary evaporator and the crude mixture was purified using flash column chromatography to afford the propargyl alcohol adduct **4** (R = Boc, R^2 = Me with 6*S* stereochemistry) (4.12 g) as oil in 60% yield. Data for **4** (R = Boc, R^2 = Me with 6*S* stereochemistry): R_f = 0.5 (silica, 2:3 ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73-4.68 (ddd, *J* = 6.04, 3.78, 1.51 Hz, 1 H, C*H*OH), 4.65- 4.62 (d, *J* = 8.31 Hz, 1 H, N*H*), 4.36-4.32 (ddd, *J* = 6.79, 5.29, 1.51 Hz, 1 H, C*H*CH_2), 4.15-4.09 (dd, *J* = 6.79, 6.04 Hz, 1 H, one of the CH_2 protons), 3.91-3.86 (dd, *J* = 6.04, 5.29 Hz, 1 H, one of the CH_2 protons), 3.83- 3.76 (m, 1 H, C*H*NH), 2.89 (bs, 1 H, O*H*), 1.45 (s, 3 H, acetonide methyl protons), 1.442 (s, 9 H, *t*-butyl protons), 1.354 (s, 3 H, acetonide methyl protons), 1.247-1.225 (d, *J* = 6.79 Hz, 3 H, CH_3).

Step 2: Preparation of the *cis*-allylic alcohol intermediate 5 (R = Boc, R^2 = Me with 6*S* stereochemistry)

Nickel acetate tetrahydrate (2.5 g) was dissolved in 95% ethanol (110 mL) and placed under H_2. A solution of $NaBH_4$ in absolute ethanol (1 M, 10 mL) was added to it under room temperature, followed after 30 minutes by ethylene diamine (2.67 mL) and compound **4** (3.0 g) dissolved in ethanol. The reaction was monitored by TLC. Upon completion, it was diluted by addition of diethyl ether and filtered through Celite pad. The organic extract was washed with brine, dried (Na_2SO_4) and concentrated. Flash chromatography of the residue afforded pure *cis*-allylic alcohol intermediate **5** (R = Boc, R^2 = Me with 6*S* stereochemistry) (2.1 g, 70% yield) as colorless oil. Data for **5** (R = Boc, R^2 = Me with 6*S* stereochemistry): R_f = 0.45 (silica, 2:3 ethyl acetate/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.62-5.55 (m, 2 H, olefinic protons), 4.92-4.68 (m, 2 H, C*H*OH), 4.36-4.27 (bs, 1 H, N*H*), 4.15-4.05 (m, 2 H, CH_2OH), 3.71-3.61 (m, 1 H, C*H*), 3.06 (bs, 1 H, O*H*), 1.44 (s, 9 H, *t*-butyl protons), 1.40 (s, 3 H, acetonide methyl protons), 1.36 (s, 3 H, acetonide methyl protons), 1.18- 1.15 (d, *J* = 6.69 Hz, 3 H, methyl protons).

Steps 3-4: Preparation of the "*cis*-2-butene-1,4-diol" intermediate 6 (R = Boc, R^2 = Me with 6*S* stereochemistry)

A solution of compound **5** (R = Boc, R^2 = Me with 6*S* stereochemistry) (1.5 g) in methanol (20 mL) was treated with CSA (1.15 g) at 0 °C. After 4 h, the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (till pH 8) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. The crude mixture was purified by flash chromatography to afford the triol (914 mg, 70% yield).

To a solution of the triol (0.843 g) in CH_2Cl_2 (15 mL) at −78 °C were added 2,4,6-collidine (0.85 mL) followed by acetyl chloride (0.25 mL). After 8 h, it was quenched by adding saturated aqueous NH_4Cl solution, extracted with ethyl acetate, washed with 1N HCl, water, brine, dried and concentrated. Column chromatography of the residue afforded pure mono acetylated "*cis*-2-butene-1,4-diol" intermediate **6** (R = Boc, R^2 = Me with 6*S* stereochemistry) (910 mg, 93% yield) as colorless oil. Data for **6** (R = Boc, R^2 = Me with 6*S* stereochemistry): R_f = 0.6 (silica, 1:9 methanol/chloroform); ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.66-5.46 (two dd, *J* = 11.89, 6.69 Hz, 2 H, olefinic protons), 4.90-4.85 (d, *J* = 8.92 Hz, 1 H, N*H*), 4.66-4.59 (dt, *J* = 6.69, 4.46 Hz, 1 H, C*H*OH), 4.41-4.36 (ddd, *J* = 6.69, 5.02, 4.46 Hz, 1 H, C*H*OH), 4.16-3.98 (two dd, *J* = 11.15, 6.69 and 11.15, 4.46 Hz, 2 H, CH_2OAc), 2.09 (s, 3 H, CH_3CO), 1.44 (s, 9 H, *t*-butyl), 1.20- 1.17 (d, *J* = 6.69 Hz, 3 H, CH_3).

STEPS 5-6: Preparation Of The Chiral Furanyl Alcohol Intermediate 7 (R = Boc, R^2 = Me With 6*s* Stereochemistry)

To a solution of compound **6** (R = Boc, R^2 = Me with 6*S* stereochemistry) (0.8 g) in CH_2Cl_2 (30 mL), pyridinium chlorochromate (PCC, 1.02 g) was added. After 30 minutes, the reaction mixture was diluted with excess diethyl ether. The organic layer was washed with 1N HCl, water, brine and dried (Na_2SO_4). After concentration, the residual oil was purified by column chromatography to give pure 2,5-disubstituted furan derivative (0.337 g, 45% yield) as colorless oil.

The resulting furan (315 mg) was dissolved in methanol (5 mL), cooled to 0 °C, and then anhydrous potassium carbonate (306 mg) was added. The reaction mixture was stirred at the same temperature for 15 minutes. It was diluted with ethyl acetate and washed with water, brine, dried (Na_2SO_4) and concentrated. Purification by column chromatography afforded the chiral furanyl alcohol intermediate **7** (R = Boc, R^2

= Me with 6*S* stereochemistry) (266 mg, 98% yield) as colorless oil. Data for **7** (R = Boc, R^2 = Me with 6*S* stereochemistry): R_f = 0.45 (silica, 1:1 ethyl acetate/hexane); $[\alpha]_D^{23}$ = –59.9 (*c* 1.76, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 6.17-6.14 (d, *J* = 2.97 Hz, 1 H, one of the ring protons), 6.08-6.04 (d, *J* = 2.97 Hz, 1 H, one of the ring protons), 4.86-4.71 (bs, 2 H, N*H* and C*H*), 4.52 (s, 2 H, CH_2OH), 2.14- 1.93 (bs, 1 H, O*H*) 1.48- 1.43 (s,12 H, *t*-butyl group and methyl protons).

STEPS 7-8: Preparation Of The Chiral Furan Amino Acid 1 (R = Boc, R^1 = Oh, R^2 = Me With 6*s* Stereochemistry)

Compound **7** (R = Boc, R^2 = Me with 6*S* stereochemistry) (260 mg) was oxidized to aldehyde in 80% yield by standard Swern oxidation procedure. A solution of oxalyl chloride (1.5 molar equiv) in dry CH_2Cl_2, cooled to – 78 °C, was treated with DMSO (3.0 molar equiv). After 5 min, the alcohol **7** (R = Boc, R^2 = Me with 6*S* stereochemistry) (1.0 molar equiv) dissolved in CH_2Cl_2 was added to the reaction mixture at the same temperature. After stirring for 1 h at –78 °C, the reaction mixture was treated with Et_3N (5.0 molar equiv), slowly warmed to 0 °C, and stirred at this temperature for 15 min. It was then poured into a cold saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Purification by column chromatography afforded the aldehyde intermediate (206 mg, 80% yield) as oil.

To a solution of the aldehyde (190 mg) in CH_3CN (4 mL) at 0 °C, sodium dihydrogen orthophosphate (174 mg) dissolved in water (1 mL) was added followed by aqueous H_2O_2 (30% w/v, 0.45 mL) and sodium chlorite (102 mg). After 4 h, the reaction mixture was quenched by aqueous 10% Na_2SO_3 solution and the reaction mixture was extracted with ethyl acetate, washed with water, brine and dried (Na_2SO_4) and concentrated. Purification by column chromatography afforded compound **1** (R = Boc, R^1 = OH, R^2 = Me with 6*S* stereochemistry) (200 mg, 98% yield) as colorless oil. Data for **1** (R = Boc, R^1 = OH, R^2 = Me with 6*S* stereochemistry): R_f = 0.45 (silica, 1:9 MeOH/$CHCl_3$ with 1% AcOH); $[\alpha]_D^{23}$ = –52.8 (*c* 1.14, MeOH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.17 (br d, *J* = 2.2 Hz, 1 H, aromatic), 6.29 (d, *J* = 2.2 Hz, 1 H, aromatic), 5.04 (br m, 1 H, N*H*), 4.93 (br m, 1 H, C*H*NH), 1.48 (d, *J* = 6.59 Hz, 3 H, CH3), 1.42 (s, 9 H, *t*-butyl).

EXAMPLE 2:

PROCESS FOR PREPARING CHIRAL FURAN AMINO ACID 1 WHEREIN C6 STEREOCHEMISTRY IS *S* AND THE SUBSTITUTIONS ARE R = BOC, R^1 = OH, $R^2 = CHME_2$

Step 1: Preparation of the propargyl alcohol adduct 4 (R = Boc, $R^2 = CHMe_2$ with 6*S* stereochemistry)

To a stirred solution of the dibromo compound **3** (6.27 g) in THF (90 mL) at −78 °C, nBuLi (1.6 M in hexane, 26 mL) was slowly added. Stirring was continued at −78 °C for 30 minutes and then at room temperature for another 30 minutes. Reaction mixture was recooled to −78 °C and the aldehyde *N*-Boc-L-valinal (**2**: R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (4.41 g), dissolved in THF (20 mL), was added. After 30 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts was washed with brine and dried over anhydrous Na_2SO_4 and filtered. The solvents were removed in rotary evaporator and the crude mixture was purified using flash column chromatography (SiO_2, 16-20% EtOAc in petroleum ether eluant) to afford the propargyl alcohol adduct **4** (R = Boc, $R^2 = CHMe_2$ with 6*S* stereochemistry) (4.06 g) as oil in 63% yield. Data for **4** (R = Boc, $R^2 = CHMe_2$ with 6*S* stereochemistry): R_f = 0.5 (silica, 40% EtOAc / Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.7 (m, 1 H, C*H*OH), 4.59 (d, J = 9.07 Hz, 1 H, N*H*), 4.12 (m, 1 H, C*H*CH_2), 3.88 (m, 2 H, CH_2), 3.54 (m, 1 H, C*H*NH), 1.78 (m, 1 H, C*H*$(CH_3)_2$), 1.46 (s, 9 H, *t*-butyl), 1.45 (s, 6 H, acetonide protons), 0.99 (d, J = 6.8 Hz, 6 H, CH_3).

Step 2: Preparation of the *cis*-allylic alcohol intermediate 5 (R = Boc, $R^2 = CHMe_2$ with 6*S* stereochemistry)

Nickel acetate tetrahydrate (2.91 g) was dissolved in 95% ethanol (129 mL) and placed under H_2. A solution of $NaBH_4$ in absolute ethanol (1 M, 11.7 mL) was added to the reaction mixture under vigorous stirring at room temperature, followed after 30 minutes by ethylene diamine (3.13 mL) and compound **4** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (3.83 g) dissolved in ethanol (15 mL). The reaction progress was monitored by TLC checking. After 1 h, reaction mixture was poured into large excess of hexane and filtered through short Celite pad and the filter cake was washed with diethyl ether. The combined organic extracts were washed with 1N HCl, water and brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Flash

chromatography (SiO_2, 18-24% EtOAc in petroleum ether eluant) of the residue afforded *cis*-allylic alcohol intermediate **5** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (2.31 g, 60% yield) as colorless oil. Data for **5** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry): R_f = 0.45 (silica, 30% EtOAc /Hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 1 H, olefinic proton), 5.54 (m, 1 H, olefinic proton), 4.71 (bs, 1 H, N*H*), 4.5 (m, 1 H, C*H*OH), 4.09 (m, 1 H, C*H*), 3.55 (m, 2 H, CH_2), 3.24 (m, 1 H, C*H*NH), 1.94 (m, 1 H, $CH(CH_3)_2$), 1.44 (s, 9 H, *t*-butyl), 1.43 (s, 6 H, acetonide methyls), 1.0 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.93 (d, *J* = 6.8 Hz, 3 H, CH_3).

Steps 3-4: Preparation of the "*cis*-2-butene-1,4-diol" intermediate 6 (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry)

A solution of compound **5** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (2.18 g) in methanol (35 mL) was treated with CSA (1.54 g) at 0 °C. After 4 h, the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (till pH 8) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude mixture was purified by flash chromatography (SiO_2, 4-6% MeOH in $CHCl_3$ eluant) to afford the *Z*-triol (1.33 g, 70% yield).

To the stirred solution of the triol (1 g) in CH_2Cl_2 (20 mL) at −78 °C were added 2,4,6-collidine (1 mL) followed by acetyl chloride (0.3 mL). After 10 h, it was quenched by adding saturated aqueous NH_4Cl solution, extracted with ethyl acetate, washed with 1N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Column chromatography (SiO_2, 3-5% MeOH in $CHCl_3$ eluant) of the residue afforded pure mono acetylated "*cis*-2-butene-1,4-diol" intermediate **6** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (928 mg, 80%) as colorless oil. Data for **6** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry): R_f = 0.45 (silica, 10% MeOH/$CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (dd, *J* = 11.33, 7.93 Hz, 1 H, olefinic proton), 5.54 (dd, *J* = 11.33, 8.31 Hz, 1 H, olefinic proton), 4.72-4.67 (m, 1 H, C*H*OH), 4.4 (dd, *J* = 7.93, 6.8 Hz, 1 H, C*H*), 4.18 (dd, *J* = 11.33, 3.4 Hz, 1 H one of the CH_2), 3.93 (dd, *J* = 11.33, 7.55 Hz, 1 H, one of the CH_2), 2.1 (s, 3 H, $COCH_3$), 2 (m, 1 H, $CH(CH_3)_2$), 1.42 (s, 9 H, *t*-butyl), 0.97 (d, *J* = 6.8 Hz, 3 H, CH_3), 0.92 (d, *J* = 6.8 Hz, 3 H, CH_3).

Steps 5-6: Preparation Of The Chiral Furanyl Alcohol Intermediate 7 (R = Boc, R^2 = $Chme_2$ With 6*s* Stereochemistry)

To a stirred solution of compound **6** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (0.9 g) in CH_2Cl_2 (32 mL), pyridinium chlorochromate (1.012 g) was added. After 30 minutes, the reaction mixture was diluted with excess diethyl ether and filtered through a short celite pad and the filter cake was washed with diethyl ether. The combined organic extracts were washed with 1N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residual oil was purified by column chromatography (SiO_2, 10% EtOAc in petroleum ether eluant) to give pure 2,5-disubstituted furan derivative (422 mg, 50%) as colorless oil.

The resulting compound (0.3 g) was dissolved in methanol (4 mL), cooled to 0 °C, and then anhydrous potassium carbonate (0.2 g) was added. The reaction mixture was stirred at the same temperature for 15 minutes. It was diluted with ethyl acetate and washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 20% EtOAc in petroleum ether eluant) afforded the chiral furanyl alcohol intermediate **7** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (245 mg, 95% yield) as colorless oil. Data for **7** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry): R_f = 0.5 (silica, 30% EtOAc/Hexane); $[\alpha]_D^{23}$ = –59.9 (*c* 1.76, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.16 (d, *J* = 2.93 Hz, 1 H, one of the furan ring protons), 6.06 (d, *J* = 2.93 Hz, 1 H, one of the furan ring protons), 4.84 (d, *J* = 8.79 Hz, 1 H, N*H*), 4.53 (s, 2 H, CH_2OH), 4.52 (m, 1 H, C*H*NH) 2.09 (m, 1 H, C$H(CH_3)_2$), 1.44 (s, 9 H, *t*-butyl), 0.94 (d, , *J* = 6.59 Hz, 3 H, CH_3), 0.88 (d, , *J* = 6.59 Hz, 3 H, CH_3).

Steps 7-8: Preparation Of The Chiral Furan Amino Acid 1 (R = Boc, R^1 = Oh, R^2 = $Chme_2$ With 6*s* Stereochemistry)

To a stirred ice-cooled solution of alcohol **7** (R = Boc, R^2 = $CHMe_2$ with 6*S* stereochemistry) (0.2 mg) in dry CH_2Cl_2 (1.6 mL) and dry DMSO (2 mL), Et_3N (0.52 mL) and SO_3-py complex (589 mg) were sequentially added. The reaction mixture was allowed to attain the room temperature slowly and stirred at the same temperature for another 1 h. After 1 h, it was quenched with saturated aqueous NH_4Cl solution, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 17-20% EtOAc in petroleum ether eluant) afforded pure aldehyde (144 mg, 85%) as colorless liquid.

To the stirred solution of the aldehyde (119 mg) in CH_3CN (4 mL) at 0 °C, $NaH_2PO_4.2H_2O$ (96.1 mg) dissolved in water (1 mL) was added followed by aqueous H_2O_2 (0.25 mL, 30% w/v) and sodium chlorite (56 mg). After 4 h, the reaction mixture was quenched by aqueous 10% Na_2SO_3 solution (2 mL) at 0 °C and the reaction mixture was extracted with ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 7-10% MeOH in Chloroform eluant) afforded compound **1** (R = Boc, R^1 = OH, R^2 = $CHMe_2$ with 6*S* stereochemistry) (110 mg, 88% yield) as white solid. Data for **1** (R = Boc, R^1 = OH, R^2 = $CHMe_2$ with 6*S* stereochemistry): R_f = 0.5 (silica, 1:9 MeOH/$CHCl_3$ with 1% AcOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (br 1 H, one of the furan ring protons), 6.39 (br, 1 H, one of the furan ring protons), 5.09 (br, 1 H, N*H*), 4.61 (br, 1 H, C*H*NH), 2.2 (m, 1 H, C*H*$(CH_3)_2$), 1.42 (s, 9 H, *t*-butyl), 0.95 (d, *J* = 6.69 Hz, 3 H, CH_3), 0.89 (d, *J* = 6.69 Hz, 3 H, CH_3).

EXAMPLE 3:

PROCESS FOR PREPARING CHIRAL FURAN AMINO ACID 1 WHEREIN C6 STEREOCHEMISTRY IS *S* AND THE SUBSTITUTIONS ARE R = BOC, R^1 = OH, R^2 = CH_2PH

Step 1: Preparation of the propargyl alcohol adduct 4 (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry)

To a stirred solution of the dibromo compound **3** (7.82 g) in THF (90 mL) at −78 °C, nBuLi (1.6M in hexane, 32.5 mL) was slowly added. Stirring was continued at −78 °C for 30 minutes and then at room temperature for another 30 minutes. Reaction mixture was recooled to −78 °C and the aldehyde *N*-Boc-L-phenylalaninal (**2**: R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (5.45 g), dissolved in THF (20 mL), was added. After 30 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts was washed with brine and dried over anhydrous Na_2SO_4 and filtered. The solvents were removed in rotary evaporator and the crude mixture was purified using flash column chromatography (SiO_2, 20-25% EtOAc in petroleum ether eluant) to afford the propargyl alcohol adduct **4** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (5.34 g, 65%) as yellow solid. Data for **4** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry): R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (m, 5 H, aromatic protons), 4.82-4.65 (m, 2 H, C*H*OH &

N*H*), 4.37 (br, 1 H, C*H*NH), 4.19-4.06 (m, 2 H, C*H* & one of the CH_2), 3.9 (m, 1 H, one of the CH_2), 2.91 (m, 2 H, CH_2Ph), 1.39-1.38 (m, 15 H, *t*-butyl & acetonide methyls).

Step 2: Preparation of the *cis*-allylic alcohol intermediate 5 (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry)

Nickel acetate tetrahydrate (2.91 g) was dissolved in 95% ethanol (129 mL) and placed under H_2. A solution of $NaBH_4$ in absolute ethanol (1 M, 11.7 ml) was added to the reaction mixture under vigorous stirring at room temperature, followed after 30 minutes by ethylene diamine (3.13 mL) and compound **4** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (4.39 g) dissolved in ethanol (15 mL). The reaction progress was monitored by TLC checking. After 1 h, reaction mixture was poured into large excess of hexane and filtered through short Celite pad and the filter cake was washed with diethyl ether. The combined organic extracts were washed with 1N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Flash chromatography (SiO_2, 22-25% EtOAc in petroleum ether eluant) of the residue afforded *cis*-allylic alcohol intermediate **5** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (2.87 g, 65% yield) as colorless oil. Data for **5** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry): R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.21 (m, 5 H, aromatic protons), 5.82-5.55 (m, 2 H, olefinic protins), 4.78 (m, 1 H, N*H*), 4.62-4.34 (m, 2 H, C*H*OH & C*H*), 4.06 (m, 1 H, C*H*NH), 3.51 (m, 2 H, CH_2), 2.85 (m, 2 H, CH_2Ph), 1.39-1.32 (m, 15 H, *t*-butyl & acetonide methyls).

Steps 3-4: Preparation of the "*cis*-2-butene-1,4-diol" intermediate 6 (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry)

A solution of compound **5** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (2.5 g) in methanol (30 mL) was treated with CSA (1.54 g) at 0 °C. After 4 h, the reaction was quenched by adding saturated aqueous $NaHCO_3$ solution (till pH 8) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude mixture was purified by flash chromatography (SiO_2, 6-8% MeOH in $CHCl_3$ eluant) to afford the *Z*-triol (1.56 g, 70% yield).

To the stirred solution of the triol (1.3 g) in CH_2Cl_2 (20 mL) at −78 °C were added 2,4,6-collidine (1 mL) followed by acetyl chloride (0.3 mL). After 10 h, it was quenched by adding saturated aqueous NH_4Cl solution, extracted with ethyl acetate,

washed with 1N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Column chromatography (SiO_2, 3-5% MeOH in $CHCl_3$ eluant) of the residue afforded pure mono acetylated "*cis*-2-butene-1,4-diol" intermediate **6** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (1.32 g, 90%) as colorless oil. Data for **6** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry): R_f = 0.45 (silica, 10% MeOH/$CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.21 (m, 5 H, aromatic protons), 5.68-5.45 (m, 2 H, olefinic protons), 4.65 (m, 2 H, C*H*OH & N*H*), 4.45 (m, 1 H, C*H*OH), 4.05 (m, 2 H, CH_2), 3.8 (m, 1 H, C*H*NH), 2.85 (m, 2 H, CH_2Ph), 2.04 (s, 3 H, COCH_3), 1.25 (m, 15 H, *t*-butyl).

STEPS 5-6: Preparation Of The Chiral Furanyl Alcohol Intermediate 7 (R = Boc, R^2 = Ch$_2$ph With 6*s* Stereochemistry)

To a stirred solution of compound **6** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (1 g) in CH_2Cl_2 (30 mL), pyridinium chlorochromate (1 g) was added. After 30 minutes, the reaction mixture was diluted with excess diethyl ether and filtered through a short celite pad and the filter cake was washed with diethyl ether. The combined organic extracts were washed with 1N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residual oil was purified by column chromatography (SiO_2, 12% EtOAc in petroleum ether eluant) to give pure 2,5-disubstituted furan derivative (455 mg, 48%) as colorless oil.

The resulting compound (300 mg) was dissolved in methanol (5 mL), cooled to 0 °C, and then anhydrous potassium carbonate (174 mg) was added. The reaction mixture was stirred at the same temperature for 15 minutes. It was diluted with ethyl acetate and washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 35-40% EtOAc in petroleum ether eluant) afforded the chiral furanyl alcohol intermediate **7** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (256 mg, 96% yield) as colorless oil. Data for **7** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry): R_f = 0.5 (silica, 40% EtOAc/hexane); ^1H NMR (200 MHz, $CDCl_3$) δ 7.2 (m, 3 H, aromatic protons), 7.02 (m, 2 H, aromatic protons), 6.12 (d, J = 2.97 Hz, 1 H, one of the furan ring protons), 5.93 (d, J = 2.97 Hz, 1 H, one of the furan ring protons), 4.94 (m, 1 H, C*H*NH), 4.81 (d, J = 8.92 Hz, 1 H, N*H*), 4.53 (s, 2 H, CH_2OH), 3.09 (d, J = 6.69 Hz, 2 H, CH_2Ph), 1.39 (s, 9 H, *t*-butyl).

STEPS 7-8: Preparation Of The Chiral Furan Amino Acid 1 (R = Boc, R^1 = Oh, R^2 = Ch_2ph With 6*s* Stereochemistry)

To a stirred ice-cooled solution of alcohol **7** (R = Boc, R^2 = CH_2Ph with 6*S* stereochemistry) (200 mg) in dry CH_2Cl_2 (1.6 mL) and dry DMSO (2 mL), Et_3N (0.44 mL) and SO_3-py complex (501 mg, 3.15 mmol) were sequentially added. The reaction mixture was allowed to attain the room temperature slowly and stirred at the same temperature for another 1 h. After 1 h, it was quenched with saturated aqueous NH_4Cl solution, extracted with ether, washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2 17-20% EtOAc in petroleum ether eluant) afforded pure aldehyde (155 mg, 78%) as colorless liquid.

To the stirred solution of the aldehyde (118 mg) in CH_3CN (4 mL) at 0 °C, $NaH_2PO_4.2H_2O$ (81 mg) dissolved in water (1 mL) was added followed by aqueous H_2O_2 (0.21 mL, 30% w/v) and sodium chlorite (47 mg). After 4 h, the reaction mixture was quenched by aqueous 10% Na_2SO_3 solution at 0 °C and the reaction mixture was extracted with ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 7-10% MeOH in Chloroform eluant) afforded compound **1** (R = Boc, R^1 = OH, R^2 = CH_2Ph with 6*S* stereochemistry) (115 mg, 92% yield) as white solid. Data for **1** (R = Boc, R^1 = OH, R^2 = CH_2Ph with 6*S* stereochemistry): R_f = 0.5 (silica, 10 MeOH/$CHCl_3$ with 1% AcOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18 (m, 5 H, aromatic protons), 7.05 (br, 1 H, one of the furan ring protons), 6.12 (br, 1 H, one of the furan ring protons), 5.03 (m, 2 H, N*H* & C*H*NH), 3.16 (m, 2 H, CH_2Ph), 1.39 (s, 9 H, *t*-butyl).

EXAMPLE 4:

PROCESS FOR PREPARING CHIRAL FURAN AMINO ACID 1 WHEREIN C6 STEREOCHEMISTRY IS *S* AND THE SUBSTITUTIONS ARE R = BOC, R^1 = OH, R^2 = PH

Step 1: Preparation of the propargyl alcohol adduct 4 (R = Boc, R^2 = Ph with 6*S* stereochemistry)

To a stirred solution of the dibromo compound **3** (6.0 g) in THF (80 mL) at –78 °C, nBuLi (1.6 M in hexane, 25 mL) was slowly added. Stirring was continued at –78 °C for 30 minutes and then at room temperature for another 30 minutes. Reaction mixture was recooled to –78 °C and the aldehyde *N*-Boc-L-phenylglycinal (**2**: R = Boc, R^2 = Ph with 6*S* stereochemistry) (3.98 g), dissolved in THF (20 mL), was added. After

30 minutes, the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4 and filtered. The solvents were removed in rotary evaporator and the crude mixture was purified using flash column chromatography (SiO_2, 16-20% EtOAc in petroleum ether eluant) to afford the propargyl alcohol adduct **4** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (3.76 g, 62%) as colorless liquid. Data for **4** (R = Boc, R^2 = Ph with 6*S* stereochemistry): R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 5.27-5.18 (m, 2 H, C*H*OH & N*H*), 5 (m, 1 H, C*H*NH), 4.94 (m, 1 H, C*H*), 4.03 (m, 2 H, CH_2), 1.44 (s, 9 H, *t*-butyl), 1.41 (s, 6 H, acetonide methyls).

Step 2: Preparation of the *cis*-allylic alcohol intermediate 5 (R = Boc, R^2 = Ph with 6*S* stereochemistry)

Nickel acetate tetrahydrate (2.41 g) was dissolved in 95% ethanol (106 mL) and placed under H_2. A solution of $NaBH_4$ in absolute ethanol (1 M, 9.7 mL) was added to the reaction mixture under vigorous stirring at room temperature, followed after 30 minutes by ethylene diamine (2.6 mL) and compound **4** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (3.5 g) dissolved in ethanol (20 mL). The reaction progress was monitored by TLC checking. After 1 h, reaction mixture was poured into large excess of hexane and filtered through short Celite pad and the filter cake was washed with diethyl ether. The combined organic extract was washed with 1N HCl, water and brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Flash chromatography (SiO_2, 20-22% EtOAc in petroleum ether eluant) of the residue afforded *cis*-allylic alcohol intermediate **5** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (2.46 g, 70% yield) as colorless oil. Data for **5** (R = Boc, R^2 = Ph with 6*S* stereochemistry): R_f = 0.45 (silica, 40% EtOAc/hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 5 H, aromatic protons), 5.87-5.55 (m, 2 H, olefinic protons), 5.25 (m, 2 H, C*H*OH, N*H*), 4.99 (m, 1 H, C*H*NH), 4.58 (m, 1 H, C*H*), 3.90 (m, 2 H, CH_2), 1.44 (s, 9 H, *t*-butyl), 1.41 (s, 6 H, acetonide methyls).

Steps 3-4: Preparation of the "*cis*-2-butene-1,4-diol" intermediate 6 (R = Boc, R^2 = Ph with 6*S* stereochemistry)

A solution of compound **5** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (2 g) in methanol (30 mL) was treated with CSA (1.28 g) at 0 °C. After 4 h, the reaction was

quenched by adding saturated aqueous $NaHCO_3$ solution (till pH 8) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The crude mixture was purified by flash chromatography (SiO_2, 6-8% MeOH in $CHCl_3$ eluant) to afford the *Z*-triol (1.25 g, 70% yield).

To the stirred solution of the triol (1 g) in CH_2Cl_2 (20 mL) at –78 °C were added 2,4,6-collidine (0.82 mL) followed by acetyl chloride (0.24 mL). After 10 h, it was quenched by adding saturated aqueous NH_4Cl solution, extracted with ethyl acetate, washed with 1N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Column chromatography (SiO_2, 3-5% MeOH in $CHCl_3$ eluant) of the residue afforded pure mono acetylated "*cis*-2-butene-1,4-diol" intermediate **6** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (961 mg, 85%) as colorless oil. Data for **6** (R = Boc, R^2 = Ph with 6*S* stereochemistry): R_f = 0.45 (silica, 10% MeOH/$CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 5.87-5.55 (m, 2 H, olefinic protons), 5.25 (m, 2 H, C*H*OH & N*H*), 4.85 (m, 1 H, C*H*NH), 4.61 (m, 1 H, C*H*OH), 4.21 (m, 2 H, CH_2), 2.1 (s, 3 H, COCH_3), 1.44 (s, 9 H, *t*-butyl).

STEPS 5-6: Preparation Of The Chiral Furanyl Alcohol Intermediate 7 (R = Boc, R^2 = Ph With 6*s* Stereochemistry)

To a stirred solution of compound **6** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (800 mg) in CH_2Cl_2 (25 mL), pyridinium chlorochromate (849 mg) was added. After 30 minutes, the reaction mixture was diluted with excess diethyl ether and filtered through a short celite pad and the filter cake was washed with diethyl ether. The combined organic extracts were washed with 1N HCl, water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. The residual oil was purified by column chromatography (SiO_2, 12% EtOAc in petroleum ether eluant) to give pure 2,5-disubstituted furan derivative (304 mg, 40%) as colorless oil.

The resulting compound (300 mg) was dissolved in methanol (5 mL), cooled to 0 °C, and then anhydrous potassium carbonate (178 mg) was added. The reaction mixture was stirred at the same temperature for 15 minutes. It was diluted with ethyl acetate and washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 35-40% EtOAc in petroleum ether eluant) afforded the chiral furanyl alcohol intermediate **7** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (248 mg, 95% yield) as colorless oil. Data for **7** (R = Boc, R^2 = Ph

with 6*S* stereochemistry): R_f = 0.45 (silica, 40% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 6.16 (d, J = 3.05 Hz, 1 H, one of the furan ring protons), 6.02 (d, J = 3.05 Hz, 1 H, one of the furan ring protons), 5.87 (br, 1 H, N*H*), 5.25 (d, J = 8.52 Hz, 1 H, C*H*NH), 4.51 (s, 2 H, CH_2OH), 1.44 (s, 9 H, *t*-butyl).

STEPS 7-8: Preparation Of The Chiral Furan Amino Acid 1 (R = Boc, R^1 = Oh, R^2 = Ph With 6*s* Stereochemistry)

To a solution of oxalyl chloride (0.09 mL) in dry CH_2Cl_2 (2 mL) at –78 °C, DMSO (0.16 mL) was added dropwise with stirring under N_2 atmosphere. After 15 min, the chiral furanyl alcohol intermediate **7** (R = Boc, R^2 = Ph with 6*S* stereochemistry) (220 mg) in dry CH_2Cl_2 (1 mL) was added to the reaction mixture. After 30 min of stirring at –78 °C, Et_3N (0.5 mL) was added and stirred at the same temperature for another 30 min, finally at the 0 °C for 0.5 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2 15-20% EtOAc in petroleum ether eluant) afforded pure aldehyde (162 mg, 75%) as colorless liquid.

To the stirred solution of the aldehyde (108 mg) in CH_3CN (4 mL) at 0 °C, $NaH_2PO_4.2H_2O$ (79 mg) dissolved in water (1 mL) was added followed by aqueous H_2O_2 (0.2 mL, 30% w/v) and sodium chlorite (46 mg). After 4 h, the reaction mixture was quenched by aqueous 10% Na_2SO_3 solution at 0 °C and the reaction mixture was extracted with ethyl acetate, washed with water, brine, dried (Na_2SO_4), filtered and concentrated in *vacuo*. Purification by column chromatography (SiO_2, 7-10% MeOH in $CHCl_3$ eluant) afforded afforded compound **1** (R = Boc, R^1 = OH, R^2 = Ph with 6*S* stereochemistry) (102 mg, 90% yield) as white solid. Data for **1** (R = Boc, R^1 = OH, R^2 = Ph with 6*S* stereochemistry): R_f = 0.5 (silica, 10% MeOH/$CHCl_3$ with 1% AcOH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.29 (m, 5 H, aromatic protons), 7.15 (br, 1 H, one of the furan ring protons), 6.21 (br, 1 H, one of the furan ring protons), 5.85 (br, 1 H, C*H*NH), 5.43 (br, 1 H, N*H*), 1.44 (s, 9 H, *t*-butyl).